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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,661	02/28/2002	Masatoshi Chiba	P21749	5687

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,661	CHIBA, MASATOSHI	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/28/02, 3/27/02, 2/27/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.00

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.Applicant's remarks and election filed 28 July 2005 have been entered.

Election/Restrictions

3. Applicant's election with traverse of Group 1 and species (a) in the reply filed on 28 July 2005 is acknowledged. The traversal is on the ground(s) that the examiner has failed to establish a search burden. This is not found persuasive because:

Applicant argues that the restriction requirement fails to mention that there would be a burden on the examiner to consider all inventions at once and thus does not meet the requirements of 35 USC §§ 121 and 372. The examiner disagrees.

35 USC § 372 states, in part:

> (b) In case of international applications designating but not originating in, the United States -
> (2) the Director may cause the question of unity of invention to be reexamined under section 121 of this title, within the scope of the requirements of the treaty and the Regulations; (emphasis added).

The instant case fits this pattern exactly. The international application designated the US, but originated in Japan. The examiner re-examined the unity of invention within the scope of the treaty. The standard to be applied in such cases is the lack of unity standard enumerated in PCT Rules 13.1 and 13.2; traditional US restriction practice does not apply in such cases. As stated on page 2 of the restriction requirement, unity of invention is lacking because Groups I and II are not drawn to the same special technical feature. Group I, claims 1 – 16 have lyophilized preparations comprising hepatocyte growth factor as their technical feature. Group II, claims 17 – 21, have stabilizing agents as their technical feature. Because the two inventions have different technical features unity of invention is lacking. Similarly, the species listed as (a) – (h) in the restriction requirement lack unity because each species is a separate chemical entity with a unique structure.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 17 – 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on 28 July 2005. Claims 1 – 16 are under examination.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action. Because the priority document is not in English, the examiner cannot determine whether it constitutes an enabling disclosure. Therefore the effective filing date of this application is set at the date the international application was filed, 31 May 2000.

Information Disclosure Statement

Applicant is advised that the English translations of the abstracts of Japanese Patent Publications listed on the IDS filed 28 February 2002 have not been received. Furthermore several applications are listed for which no translation is listed or provided.

Claim Objections

7. Claims 4 – 6 are objected to because of the following informalities: the claims recite multiple non-elected species. Appropriate correction is required.

8.

Claim Rejections - 35 USC §§ 102 and 103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 – 9, and 12 – 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (European Patent Application 0456188A1, published 13 November 1991, cited on IDS filed 27 March 2002). Nakamura teaches a lyophilized preparation comprising the following components: 1 mg HGF, 100 ml of phosphate buffer, 0.15 M NaCl (see column 14, lines 25 – 35). Nakamura teaches stabilizing agents which can be added to the HGF preparation prior to lyophilization (see column 9 line 52 – column 10 line 13). The preparation contained 0.01 mg /ml of HGF, and is to be reconstituted at 0.01 mg/ml. Thus the prior art lyophilized preparation meets the limitations of claims 1 – 3 as it contains all the components recited in the claims and Nakamura gives guidance as to how the product is to be reconstituted. Nakamura also teaches that arginine can be used as the stabilizing agent (see column 9 lines 52 – 58), meeting the limitations of claims 4 – 6. Phosphate buffer is a phosphoric acid salt, and thus Nakamura also teaches the limitations of claim 7.

Nakamura teaches phosphate buffer with pH 7.4 and 0.15 M NaCl, which are desirable for injection. The specification provides examples using 0.14 M (examples 2 and 3, p. 11) and 0.30 M NaCl (see examples 4 and 5, p. 12) and since the prior art teaching is within the range of what applicant considers to be an acceptable concentration of NaCl, the osmostic pressure is deemed to be desirable as an injection. Since lyophilization removes water from the composition, the pH and osmotic pressure after reconstitution with water will be the same as those that were present before lyophilization. Thus Nakamura inherently teaches the limitations of claims 8 and 9.

Nakamura also teaches adding Polysorbate 80 to the composition before lyophilizing (see column 14 lines 25 – 35) and applicant explicitly includes Polysorbate 80 in the definition of surface active agents (specification, p. 9, final paragraph) thus the reference also meets the limitations of claim 12. The specification defines Polysorbate 80 as a polyoxyethylene ether (see sentence spanning pp. 9 – 10) and thus the teachings of Nakamura also meets the limitation of claims 13 – 14. Nakamura teaches preparing the lyophilized preparation in an ampoule (see column 14 line 33) meeting the limitation of claim 15.

11. Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nakamura. The reasons why the teachings of Nakamura meet the limitations of claim 1 are presented in the previous paragraphs. Claim 16 is drawn to an amount of the stabilizing agent sufficient to prevent HGF aggregate formation

during lyophilization and/or storage after lyophilization. The examiner cannot determine if the amount used by Nakamura is sufficient to achieve the claimed property, prevention of aggregate formation.

12. Claims 1 – 3, 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanaka et al. (WO 97/02832, published 30 January 1997), as evidenced by Tanaka et al. (U.S. Patent Application Publication 2001/0051604, published 13 December 2001, cited by applicant on IDS filed 27 February 2004). The U.S. Patent Application Publication is the national stage entry of the PCT application that was published as WO 97/02832). Since 35 USC § 372(b)(3) requires that the application be submitted in English upon entry to the national stage, the '604 publication is a proper translation of the earlier Japanese document. The page and paragraph numbers cited herein are from the '604 publication but the same information was disclosed in Japanese in the earlier WIPO publication.

Tanaka teaches lyophilized preparation of lyophilized HGF, wherein the composition before lyophilization comprises HGF, sodium chloride, and a buffering agent (see p. 2, paragraph 0025; see also paragraph 0017 for a list of stabilizers and paragraph 0018 for a list of buffers). It is acknowledged that Tanaka teaches 20 mg/ml HGF rather than 5 mg/ml HGF as recited in claim 1. However this is a product-by-process limitation and therefore does not receive patentable weight. Thus Tanaka teaches all the limitations of claim 1. Claim 2 recites an intended use, namely preparation of an aqueous solution but intended uses are not given patentable weight. Claim 3 recites both the product-by-process and intended use limitations. Since Tanaka teaches the composition and lyophilization, the reference meets the limitations of claims 1 – 3. Tanaka teaches phosphate buffer as the buffering agent, and since this is a phosphoric acid salt it meets the limitations of claim 7. Tanaka teaches pH 7.0 buffer (see p. 3 paragraph 0028) and teaches osmotic pressure ratio suitable for injection (see p. 2 paragraph 0020) meeting the limitation of claim 8. Since lyophilization removes water from the composition, the pH and osmotic pressure after reconstitution with water will be the same as those that were present before lyophilization. Thus Tanaka inherently teaches the limitations of claims 8 and 9. Tanaka also teaches sodium citrate as the buffer wherein the pH is 5.0 to 6.0 (see p. 2 paragraph 0018), meeting the limitations of claims 10 – 11. Tanaka teaches the lyophilized composition with polysorbate 80 (see paragraph 0025), which meets the limitations of claim 12 – 14 as the specification discloses that polysorbate 80 is a polyoxyethylene ether surface active agent (see sentence spanning pp. 9 – 10 of specification). Tanaka also teaches

administering the composition to a vial before lyophilizing (see paragraph 0025), meeting the limitation of claim 15.

13. It noted that while Tanaka does not teach arginine, to which the search was limited, as a stabilizing agent, the reference does teach other non-elected stabilizing agents including sulfated polysaccharides recited in claim 4 (see paragraph 0017 of Tanaka).

14. Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tanaka et al. The reasons why the teachings of Tanaka meet the limitations of claim 1 are presented in the previous paragraphs. Claim 16 is drawn to an amount of the stabilizing agent sufficient to prevent HGF aggregate formation during lyophilization and/or storage after lyophilization. The examiner cannot determine if the amount used by Tanaka is sufficient to achieve the claimed property, prevention of aggregate formation, although it is noted that Tanaka teaches aggregate formation is associated with decreased biological activity (paragraph 0006) but the lyophilized preparations do not show decreased biological activity (see paragraph 0034), suggesting the amount of stabilizing agent is sufficient to prevent aggregate formation.

15. Claims 1 – 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura (European Patent Application 0456188A1), in view of Tanaka et al. (WO 97/02832, published 30 January 1997), as evidenced by Tanaka et al. (U.S. Patent Application Publication 2001/0051604, published 13 December 2001, cited by applicant on IDS filed 27 February 2004). The U.S. Patent Application Publication is the national stage entry of the PCT application that was published as WO 97/02832). Since 35 USC § 372(b)(3) requires that the application be submitted in English upon entry to the national stage, the '604 publication is a proper translation of the earlier Japanese document. The page and paragraph numbers cited herein are from the '604 publication but the same information was disclosed in Japanese in the earlier WIPO publication.

The reasons why the teachings of Nakamura are deemed to meet the limitations of claims 1 – 9 and 12 – 15 are provided in paragraph 9. Nakamura does not teach the pH of the aqueous solution between 5.0 and 6.5. Tanaka teaches preparation of lyophilized HGF wherein the pH of the solution before lyophilization is between 5.0 and 6.5, and further comprising stabilizing agents including amino acids (see page 2, paragraph 0017), and buffering agents to keep the pH in the desired range. Specifically, Tanaka teaches buffers comprising citrate, where in the pH is between 5.0 to 6.0 (see page 2, paragraph 0018). Tanaka teaches that

keeping the pH between 5.0 and 6.0 is advantageous, as HGF shows increased solubility at this pH. Thus the teachings of Tanaka meet the limitations of claims 10 and 11. Tanaka also teaches that lyophilization according to their disclosed method is sufficient to prevent aggregate formation (see page 1, paragraph 0006), meeting the limitations of claim 16.

It would have been prima facie obvious to one of ordinary skill in the art to make the lyophilized preparation of Nakamura using the buffer with pH 5.0 – 6.5 as taught by Tanaka, with a reasonable expectation of success. Tanaka teaches that the lower pH range is advantageous, as HGF is more soluble in the more acidic environment. Therefore one of ordinary skill in the art would be able to make the preparation faster, as it would take less time for the HGF to dissolve. It would be reasonable to expect success, as both references are drawn to the same subject matter, namely preparation of lyophilized HGF and use of multiple buffer systems is within the skill of the ordinary artisan.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
August 11, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
8-15-05